

September 24, 2004

Dr. Deborah Drechsler, Ph.D.
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**RE: Written Comments on Chapter 10, Quantifying the Health Benefits of
Reducing Ozone Exposure, of the Draft Staff Report on the CA Ozone
Ambient Air Quality Standards**

Dear Dr. Drechsler:

Attached for your review and inclusion in the public comment record are comments on Chapter 10 of the Draft Staff Paper on ozone prepared on behalf of the Engine Manufacturers Association (EMA). The review comments on the Health Benefits Chapter were prepared by Dr. Suresh Moolgavkar of the University of Washington and examine the assumptions and conclusions reached in the chapter. These comments supplement our written comments previously submitted on the Draft Staff Paper.

EMA would appreciate your efforts to forward copies of Dr. Moolgavkar's comments to the Air Quality Advisory Committee in advance of their review of the document.

As noted in our original submittal, the scientific literature regarding the health effects of ambient ozone often provides inconsistent findings, particularly from epidemiology studies where any small effects of ozone on populations are difficult to isolate from other confounding variables. As Dr. Moolgavkar points out in the attached comments, the epidemiology studies that are used to estimate health effects from ozone in Chapter 10 appear to be insufficient to assure any reliable estimates or benefits of reducing current ambient ozone levels. These uncertainties are not adequately discussed in Chapter 10.

Additionally, the recently published paper from the Children's Health Study in southern California reinforces EMA's previous comments that there is little evidence to support the conclusions of significant health effects from ambient levels of ozone, much less attempt to quantify them. The considerable uncertainties and varied results found in epidemiological studies of ozone need to be better addressed in Chapter 10 and the entire Draft Staff Paper. These issues need to be adequately addressed before the issue of establishing new ambient ozone standards can be resolved.

Please feel free to contact me if you have any questions regarding the attached comments.

Sincerely,

Joseph L. Suchecki
Director, Public Affairs

Review of Chapter 10

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Chapter 10 of the California Document estimates the health benefits that would be expected to accrue from a roll-back of ozone concentrations to the proposed new standards. It should be recognized that such estimates depend on a number of assumptions. The first and the most important assumption is that the associations reported in epidemiological studies are causal. Particularly when estimated risks from observational epidemiological are small there is real concern that the results could be due to residual confounding. This is particularly true for air pollution epidemiology where the estimated risks are miniscule. As a whole, the California Document fails to acknowledge the extent to which the results of epidemiological studies of air pollution depend upon model choice, which includes choice of lag structure, control of weather and temporal trends, and inclusion of copollutants. Indeed, as an HEI expert panel noted, there is no statistical methodology that could guarantee that weather and temporal trends have been adequately adjusted. In a recent paper, Thurston and Ito (2001) showed that the estimated ozone effects on mortality were sensitive to the way in which temperature was controlled. Recent discussions of model choice in air pollution epidemiology have focused on particulate matter (PM). However, the lessons are clear. As Koop and Tole (2004), commenting on time-series studies, say, “The main empirical finding of the paper is that standard deviations for air pollution-mortality impacts become very large when model uncertainty is incorporated into the analysis. Indeed they become so large as to question the plausibility of the previously measured links between air pollution and mortality.” It is clear that the uncertainty in the estimates of pollutant associations with health effects in human populations greatly exceeds the statistical uncertainty captured by the 95% confidence intervals generated by specific models used for data analyses. Chapter 10 should explicitly acknowledge the large uncertainties introduced by model choice and, specifically, that no inference of causality can be made from the reported associations between ozone and mortality in epidemiological studies.

Concentration-Response Functions in Chapter 10

Shape of the C-R functions

The C-R functions in chapter 10 are derived from time-series studies and, with the exception of the C-R function for emergency room visits for asthma, assumed to be linear functions with no thresholds. The C-R function for emergency room visits for asthma, by contrast, is assumed to have a threshold. The chapter says, “These latter studies, reviewed in Section 8.3.3.2 suggest a population threshold in the range of 0.075 to 0.110 ppm for 1hr exposures, and 0.056 to 0.084 ppm (using a ratio of 1.33) for 8-hour exposures (see pg. 8-14; figure 8-1).” This result would appear to be contrary to expectation. Asthma is often considered to be the sentinel condition for ozone exposure. If the associations

between ozone exposure and health effects are causal, one would expect a causal pathway from exacerbation of asthma to emergency room visits to hospital admissions and finally death. One would not expect to see a non-threshold linear C-R function for the most serious health end points with a threshold C-R function for the less serious health end point. Thus it is counter-intuitive to see a linear non-threshold C-R function for hospital admissions and mortality in the presence of a threshold for emergency room visits for asthma.

In fact, there has been little systematic examination of the issue of thresholds in time-series studies of C-R functions for ozone. In a recent paper employing GAM models, however, Moolgavkar (2003) showed that the C-R functions for ozone and mortality in Los Angeles and Chicago were highly non-linear and, moreover, had shapes that were not consistent with reasonable biological hypotheses regarding plausible modes of action of ozone. One long-term study of air pollution and mortality, the Veterans Study (Lipfert et al., 2000), suggested a threshold for ozone-associated mortality at 0.14 ppm. This finding is difficult to reconcile with the non-threshold C-R functions used in chapter 10. It is also puzzling that time-series studies report associations between ozone and daily mortality, but large long-term studies, such as the Harvard Six Cities and the ACS II studies, including updates of these studies, do not report such associations despite the high ambient levels of ozone when these studies were instituted. If the associations between ozone and mortality in time-series studies were causal one would expect to see similar positive associations in these long-term studies.

In conclusion, there is little evidence to support the use of a specific exposure-response relationship for ozone. The non-threshold linear relationship is often used as a default by regulatory agencies because it is considered to be protective of public health.

Coefficients

To estimate the benefits from a roll-back of ozone levels to the proposed guidelines, the California Document uses estimated coefficients for a number of health end points in the linear C-R functions. Since the results of studies are not always reported using identical ozone metrics, the chapter first uses conversion factors to translate metrics into a common set. Specifically, the authors of the chapter say, “Most health studies considered in our analysis were conducted with ozone levels measured as 1-hour maximum or 8-hour maximum. However, there were some studies that measured ozone averaged over other time increments. Since these studies were conducted throughout the United States and other parts of the world, a national average of adjustment factors were used to convert all measurements to 1-hour and 8-hour averages (Schwartz 1997). The 1-hour maximum was assumed to be 2.5 times the 24-hour average, and 1.33 times the 8-hour average concentration. These conversion factors have been used in previous meta-analyses of the ozone epidemiological literature (Levy et al., 2001; Thurston and Ito 2001).” Clearly, these single conversion factors are highly imprecise and introduce even more uncertainty into the computations presented in chapter 10. No mention is made of this uncertainty. The use of these conversion factors by others in the past does not justify their use here.

A number of estimates of effect used in the C-R functions are consensus estimates derived from meta-analyses reported in the literature. Whether the coefficients derived from these analyses are relevant to the California situation is not clear. A priori on biological grounds it is reasonable to believe that, even if ozone is causally associated with health end points, the magnitude of ozone effects are likely to be different in different geographic areas because of different weather and pollution profiles. Additionally, since time-series studies estimate a population relative risk, the estimate will depend on the distribution of susceptible individuals in the population, which undoubtedly varies by geographic area. Thus, interpretation of meta-analyses that report a single consensus estimate of risk from multiple studies conducted in different geographic areas is highly problematic.

The most serious health end point that has been associated with ozone is death. As noted above, the epidemiological studies of air pollution provide little evidence that the reported associations between ozone and mortality are causal. Nonetheless, the coefficients derived from these studies can be used to estimate the number of deaths that could be averted with a rollback of ozone levels under the assumption that the association is causal. The central issue then is the choice of an appropriate coefficient. Although many US time-series studies of ozone and mortality are available, including NMMAPS, arguably the most comprehensive time-series study of air pollution ever conducted, the California Document surprisingly uses a coefficient reported in a WHO document (2004) and derived from a meta-analysis in Europe to estimate the number of deaths that could be avoided by rolling back ozone concentrations to the proposed levels. NMMAPS, which included the 90 largest metropolitan areas in the US, used a unified approach to time-series analyses in the different locations. Moreover, reanalyses were conducted after discovery of the S-plus convergence problems. It is not clear that the European studies were reanalyzed to address the convergence problem; reanalyses would be expected to yield smaller coefficients. There are other problems of interpretation in using the WHO meta-analysis coefficient. If a causal ozone association exists, from a biological perspective one would expect that ozone exposure is more strongly associated with respiratory mortality than with general non-accidental mortality. Yet the WHO report finds no association between ozone and respiratory mortality. Similarly one would expect to find a stronger association between ozone and cardiovascular mortality than total mortality. Here again the WHO reports similar coefficients for total and cardiovascular mortality. In view of these findings, which are quite contrary to biological expectation and argue against a causal interpretation of the reported associations, the WHO coefficient for total mortality is probably a poor choice for estimating the mortality associated with exposure to ozone in California.

If the ARB insists on estimating the number of deaths averted even in the absence of evidence of causality, it is difficult to understand why the document did not use the coefficient derived from NMMAPS. The chapter argues that NMMAPS probably underestimates risk, because of the way weather is addressed in the study. Since there is really no objective information on how confounding by weather should be addressed, it could be equally well argued that NMMAPS and other time series studies overestimate

the association of ozone with health outcomes. NMMAPS is the only study to use a unified approach to analyses of the largest metropolitan areas in the US. It would seem, moreover, that a coefficient derived from analyses of US cities would be more relevant to the California situation than a coefficient derived from a consideration of European cities. If the NMMAPS coefficients were used under the assumption that the associations are causal, the estimate and analysis of mortality in the chapter would be quite different.

The California Document fails to note also that the WHO report discusses the possibility of publication bias in the air pollution literature. Specifically, for studies of associations between ozone and mortality, whether all-cause or respiratory mortality, the report clearly finds evidence of publication bias in that negative studies were likely not published. The WHO report attempts to correct this bias by using the ‘trim and fill’ technique and finds that the coefficients for both all-cause and respiratory mortality decrease when publication bias is corrected in this way. Specifically, the coefficient for respiratory mortality becomes negative, i.e., the relative risk is less than 1, and the coefficient for all-cause mortality decreases by a third. Thus, the results of the analysis would be considerably different if these bias-corrected coefficients were used in place of the original coefficients, and the lower confidence bound would include zero.

Although the WHO report also presents results of meta-analyses of the association between ozone and hospital admissions the California Document ignores these results and chooses instead to use the coefficient from a contributed book chapter by Thurston & Ito. For one thing, this book chapter is not a peer-reviewed publication and for another the coefficient derived there is based on 3 old studies conducted in the mid-nineties. By contrast, the WHO report presents results of hospital admissions for respiratory causes in two broad age-groups, 15-64 and 65+. Each of these coefficients is based on 5 studies. These coefficients translate roughly to an increase in hospital admissions for respiratory causes of 0.15% and 0.75% per 100 ppb increase in 1-hour ozone for the age groups 15-64 and 65+ respectively, considerably smaller than the 1.65% figure used in chapter 10. Moreover, both WHO estimates are statistically non-significant so that if these estimates were used, the lower bound on the number of hospital admissions avoided would include zero.

Chapter 10 assumes that there is a threshold for ozone-associated emergency room visits for asthma. Biological considerations would then imply, as mentioned earlier, that thresholds should also exist for more serious health end points such as hospital admissions and deaths. For emergency room visits for asthma, school absences and minor restricted activity days (MRAD), the authors of chapter 10 derive the coefficients used to estimate the benefits that would be expected to accrue from a roll back of ozone concentrations. Not enough detail is provided in the discussion of these conditions to comment on the appropriateness of these coefficients.

Summary

Chapter 10 makes a number of assumptions and choices in estimating the number of health events that would be avoided by rolling back ozone concentrations to the

proposed new standards. The most crucial assumptions are that the associations reported in epidemiological studies are causal and that the C-R relationship is linear without a threshold. The most critical choice is the choice of the coefficients used in the C-R functions. The assumption of a non-threshold linear relationship finds little support in the literature as the issue has not been systematically addressed, but this assumption may be reasonable on the basis of the precautionary principle. The choice of coefficients is not well justified, with the coefficient for mortality taken from European studies, that for hospital admissions from US studies, and other coefficients derived by the authors of the chapter without sufficient description of the procedures used. In general, chapter 10 gives the impression that the coefficients have been selected so as to maximize the estimated benefits from ozone reductions. Given the large uncertainties in the epidemiological literature it is premature to attempt to estimate the benefits that would accrue from rolling ozone concentrations back to the proposed levels. If, however, ARB insists on making such estimates, at the very least chapter 10 should be revised to discuss clearly the assumptions made, including the assumption of causality, and to justify better the choice of the C-R functions and coefficients used.

References

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